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EXAMINER	
FORMAN, BETTY J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/449,204	Applicant(s) SINICROPI ET AL.	
	Examiner BJ Forman	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _01 April 2004_.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _2,4,5,8-14,17-20 and 24-69_ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _2,4,5,8-14,17-20 and 24-69_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _4/04_.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1 April 2004 has been entered.

Status of the Claims

2. This action is in response to papers filed 1 April 2004 in which new claims 47-69 were added and the previous rejection was traversed. The new claims have been thoroughly reviewed and entered. The previous rejections in the Office Action dated 10 March 2003 are maintained. All of the arguments have been thoroughly reviewed and are discussed below. New grounds for rejection, necessitated by the added claims are discussed.

Claims 2, 4-5, 8-14, 17-20 and 24-69 are under prosecution.

Claim Rejections - 35 USC § 112

35 U.S.C. 112: First Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 24-36, 38-41, 43-45, 61-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to target molecules of various concentrations from equal or less than 1pg/ml (which encompasses 0) to 1000pg/ml and various concentration ranges of 0.03-5000pg/ml. The specification teaches concentration ranges of 0.005-5000pg/ml and preferably 1-1000pg/ml (page 23, lines 31-34). The specification also teaches detection of a single target i.e. VEGF with a sensitivity of 1000-0.031pg/ml (page 36, lines 3-4). However, the specification does not teach or suggest the concentrations (encompassing 0) and/or ranges instantly claimed. Regarding a subgenus range the courts have stated that a subgenus range is not necessarily described in the specification.

> "Thus, the written description requirement prevents an applicant from claiming subject matter that was not adequately described in the specification as filed. New or amended claims which introduce elements or limitations which are not supported by the as-filed disclosure violate the written description requirement. See, e.g., In re Lukach, 442 F.2d 967, 169 USPQ 795 (CCPA 1971) (subgenus range was not supported by generic disclosure and specific example within the subgenus range); In re Smith, 458 F.2d 1389,1395, 173 USPQ 679, 683 (CCPA 1972) (a subgenus is not necessarily described by a genus encompassing it and a species upon which it reads)."

35 U.S.C. 112: Second Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 24-26 and 61-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the phrase "less than about 1000 (100 and/or 1) pg/ml". The phrase "less than" typically indicates a maximum point. The phrase "less than" however, is contraverted by the term "about" which implies that values above and below 1000 (100 and/or 1) pg/ml are permitted. Further, the extent of variance permitted by "about" is unclear in this context because it is also unclear if "about 1000" simply includes 1010 or if it also includes 1000-1500 as well. In Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (CAFC 1991), the CAFC stated, "The district court held claims 4 and 6 of the patent invalid because their specific activity limitation of "at least about 160,000" was indefinite". After review, the CAFC states "We therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase "at least about" indefinite where the metes and bounds of the term were not defined in the specification.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 2, 4-5, 8-14, 17-20 and 24-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hendrickson et al. (Nucleic Acids Research, 1995, 23(3): 522-529) in view of Gibson et al. (Genome Methods 1996, 6: 995-1001) and Gold et al. (U.S. Patent No. 5,475,096, filed 10 June 1991).

Regarding Claim 46, Hendrickson et al. teach a method for quantitating or detecting the presence of a target compound in a sample, the method comprising: exposing the sample to a capture molecule which binds to the target molecule to form a capture molecule-target molecule complex, adding to the complex a nucleic acid moiety containing a detector molecule wherein the detector molecule binds to the target molecule to form a capture molecule-target molecule-detector molecule complex, washing the complex to remove test materials (e.g. nuclease), amplifying the nucleic acid moiety by PCR amplification, and quantitating or detecting the PCR amplified nucleic acid moiety (page 523, Fig. 1). Hendrickson et al. do not teach that the detector molecule is an aptamer and they do not teach that the amplified aptamer is quantitated or detected using a detectable non-primer probe and real-time PCR.

However, real-time PCR using detectable non-primer probes was also well known and routinely practiced in the art at the time the claimed invention was made as taught by Gibson et al. Specifically, Gibson et al. teach a method for detecting a PCR amplified product with sequence-specific non-primer probes using real-time PCR (page 997, right column, page 1000, last paragraph and Table 1) wherein the reaction is detected and quantitated every 8.5 seconds thereby providing accurate and time-sensitive information during the PCR reaction (page 996, left column, lines 1-3). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the detection of Hendrickson et al. wherein aliquots of the PCR reaction are run on agarose gel for detection and quantitation of amplified product

at a single time point (page 525, right column, second full paragraph) with the Gibson et al. method wherein the PCR reaction is detected and quantitated every 8.5 seconds (page 996, left column, lines 1-3) by detection of non-primer probe hybridization for the expected benefit of eliminating the agarose gel step and for the expected benefit of accurate and time-sensitive detection as taught by Gibson et al. (page 995, right column, lines 1-5).

Additionally, aptamer detector molecules were well known in the art at the time the claimed invention was made as taught by Gold et al. (Column 8, lines 22-45) who teach that aptamers can be employed as antibodies; aptamers have conventionally been employed in detection assays; and aptamers have numerous advantages over antibodies i.e. aptamers can be readily amplified, they do not require animal immunization and the binding affinity of aptamers can be tailored to users needs (Column 8, lines 37-45). Therefore, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the antibody-detector molecule of Hendrickson et al. with the aptamer-detector molecule of Gold et al. for the expected benefit of specific, qualitative and quantitative detection of target molecules as taught by Gold et al. (Column 27, lines 54-56) and for the additional benefits of aptamers i.e. aptamers can be readily amplified, they do not require animal immunization and the binding affinity of aptamers can be tailored to used needs as taught by Gold et al. (Column 8, lines 37-45).

Regarding Claim 2, Hendrickson et al. teach the method further comprising washing the capture molecule-target molecule complex to remove unbound sample after step (a) (page 525, left column, third full paragraph, lines 5-6).

Regarding Claim 4, Hendrickson et al. teach the method wherein the capture molecule is bound to a solid support (page 1372, Fig. 1).

Regarding Claim 5, Hendrickson et al. teach the method wherein the capture molecule is bound to a solid support (page 1372, Fig. 1) but they do not teach the method wherein the capture molecule is in solution during step (a) or (b). However, binding of capture molecule-

target molecules in solution was routinely practiced in the art. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the immobilized capture of Hendrickson et al. with capture molecules in solution for the known benefit of binding capture-to-target molecules in large volumes for the obvious benefit of more rapid binding in solution as known in the art.

Regarding Claim 8, Hendrickson et al. teach the method wherein the target molecule is an organic compound having a molecular weight of about 100 to about 1000 grams/mole i.e. human thyroid stimulating hormone (hTSH) (page 523, left column, second full paragraph, lines 1-3).

Regarding Claim 9, Hendrickson et al. teach the method of wherein the target molecule is a protein i.e. hTSH (page 523, left column, second full paragraph, lines 1-3).

Regarding Claim 10, Hendrickson et al. teach the method of wherein the target molecule is a protein i.e. hTSH (page 523, left column, second full paragraph, lines 1-3).

Regarding Claim 11, Hendrickson et al. do not teach the method wherein the sample is selected from the group consisting of blood, serum, sputum, urine, semen, cerebrospinal fluid, bronchial aspirate and organ tissue. However, Hendrickson et al. teach the method detects hTSH known to be present in blood (page 526, left column, last paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the method for detecting hTSH is a sample as taught by Hendrickson et al. to samples known to contain hTHS for the expected benefit of highly sensitive detection of hTSH (a clinically important target molecule) in blood as taught by Hendrickson et al. (page 528, last paragraph).

Regarding Claim 12, Hendrickson teach the method wherein the capture molecule is immobilized on a solid support (page 525, left column, second full paragraph, lines 1-6) but they do not teach the immobilization is via biotin labeled capture molecule bound to a streptavidin or avidin labeled support. However, biotin-labeled capture molecules immobilized via binding to a streptavidin or avidin labeled support were known and routinely practiced in

the art at the time the claimed invention was made. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the immobilization of Hendrickson et al. with routinely practiced biotin-avidin immobilization for the known benefit of rapid and specific biotin-avidin immobilization.

Regarding Claims 13-14, Hendrickson et al. do not teach quantitation or detection using a non-primer probe having a fluorescent dye label (Claim 13) wherein the fluorescent dye label comprises two dyes (Claim 14). However, Gibson et al. teach quantitation of the amplified nucleic acid moiety using a detectable non-primer probe having a fluorescent dye label (page 996, right column lines 1-4) wherein the fluorescent dye label comprises two dyes, a reporter dye and a quencher dye which fluoresce at different wavelengths (page 996, right column lines 1-16). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the detection of Hendrickson et al. with the two-dye fluorescent detection of Gibson et al. wherein fluorescently labeled non-primer probes are detected to quantitate PCR product by monitoring fluorescence emission and quenching (page 996, right column, lines 1-16) for the obvious benefit of detecting and quantitating amplified product over an extended period of time and for the expected benefit of accurate and time-saving detection as taught by Gibson et al. (page 995, right column, lines 1-5).

Regarding Claims 17-19, Hendrickson et al. do not teach the detector molecule is RNA and the RNA is reverse transcribed to form DNA before or during amplifying (Claim 17), at a temperature sufficient to dissociate the detector molecule (Claim 18) and at a temperature about 50 to about 70°C (Claim 19). However, Gold et al. teach aptamers are RNA (Column 14, lines 34-35) which are reverse transcribed before amplifying (Column 13, lines 39-51). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA of Hendrickson et al. with RNA as taught by Gold et al. based on target to be detected and desired results and to reverse transcribed the RNA to DNA before amplification as taught by Gold et al. and for the expected benefits of amplification using the

polymerase chain reaction (Gold et al., Column 13, lines 40-42). Additionally, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to reverse transcribe the RNA detector molecule at a temperature sufficient to dissociate the detector molecule and specifically between 50 and 70°C for the obvious benefit of transcribing the RNA at temperature which prevents secondary structure of the RNA and for the expected benefit of partitioning the RNA detector molecule for identification as taught by Gold et al. (Column 1, lines 14-31).

Regarding Claim 20, Hendrickson et al. teach the method wherein the solid support is a 96-well thermowell microtitre plate which is placed into a thermal cycler for PCR amplification (page 525, left column, second full paragraph, lines 1-4 and fourth paragraph, lines 1-3) but they do not teach the solid support is a PCR tube. However, 96-well microtitre plates and PCR tubes were known and routinely practiced in the art for one-well/sample and one-tube/sample wherein reagent mixing and nucleic acid amplification for each sample is in isolation. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 96-wells PCR solid support of Hendrickson et al. with a single-well PCR solid support based the number of samples to be assayed, available equipment and experimental design for the obvious benefit of reducing the cost and labor involved with 96-format assays by performing single-format assays.

Regarding Claims 24-45, Hendrickson et al. teach the method wherein the target molecule is quantitated at a concentration equal to or less than 1 pg/mL (Claims 14-16) about 100 to about 5000 pg/ml (Claims 27-29); of about 3 to 100 pg/ml (Claims 30-32); of about 0.4 to about 100pg/ml (Claims 33-35); of about 1 to about 100 pg/ml (Claims 36-38); of about 0.03 of about 100 pg/ml (Claims 39-41); of about 0.005 to about 1 pg/ml (Claims 42-44) (page 526, right column, first full paragraph and Fig. 4).

Regarding Claim 47, Hendrickson et al. teach a method for quantitating or detecting the presence of a target compound in a sample, the method comprising: exposing the sample to a

capture molecule which binds to the target molecule to form a capture molecule-target molecule complex, adding to the complex a nucleic acid moiety containing a detector molecule wherein the detector molecule binds to the target molecule to form a capture molecule-target molecule-detector molecule complex, washing the complex to remove test materials (e.g. nuclease), amplifying the nucleic acid moiety by PCR amplification, and quantitating or detecting the PCR amplified nucleic acid moiety (page 523, Fig. 1). Hendrickson et al. do not teach that the detector molecule is an aptamer and they do not teach that the amplified aptamer is quantitated or detected using a detectable non-primer probe and real-time PCR.

However, real-time PCR using detectable non-primer probes was also well known and routinely practiced in the art at the time the claimed invention was made as taught by Gibson et al. Specifically, Gibson et al. teach a method for detecting a PCR amplified product with sequence-specific non-primer probes using real-time PCR (page 997, right column, page 1000, last paragraph and Table 1) wherein the reaction is detected and quantitated every 8.5 seconds thereby providing accurate and time-sensitive information during the PCR reaction (page 996, left column, lines 1-3). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the detection of Hendrickson et al. wherein aliquots of the PCR reaction are run on agarose gel for detection and quantitation of amplified product at a single time point (page 525, right column, second full paragraph) with the Gibson et al. method wherein the PCR reaction is detected and quantitated every 8.5 seconds (page 996, left column, lines 1-3) by detection of non-primer probe hybridization for the expected benefit of eliminating the agarose gel step and for the expected benefit of accurate and time-sensitive detection as taught by Gibson et al. (page 995, right column, lines 1-5).

Additionally, aptamer detector molecules were well known in the art at the time the claimed invention was made as taught by Gold et al. (Column 8, lines 22-45) who teach that aptamers can be employed as antibodies; aptamers have conventionally been employed in detection assays; and aptamers have numerous advantages over antibodies i.e. aptamers can

be readily amplified, they do not require animal immunization and the binding affinity of aptamers can be tailored to users needs (Column 8, lines 37-45). Therefore, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the antibody-detector molecule of Hendrickson et al. with the aptamer-detector molecule of Gold et al. for the expected benefit of specific, qualitative and quantitative detection of target molecules as taught by Gold et al. (Column 27, lines 54-56) and for the additional benefits of aptamers i.e. aptamers can be readily amplified, they do not require animal immunization and the binding affinity of aptamers can be tailored to used needs as taught by Gold et al. (Column 8, lines 37-45).

Regarding Claim 48, Hendrickson et al. teach the method further comprising washing the capture molecule-target molecule complex to remove unbound sample after step (a) (page 525, left column, third full paragraph, lines 5-6).

Regarding Claim 49, Hendrickson et al. teach the method wherein the capture molecule is bound to a solid support (page 1372, Fig. 1).

Regarding Claim 50, Hendrickson et al. teach the method wherein the capture molecule is bound to a solid support (page 1372, Fig. 1) but they do not teach the method wherein the capture molecule is in solution during step (a) or (b). However, binding of capture molecule-target molecules in solution was routinely practiced in the art. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the immobilized capture of Hendrickson et al. with capture molecules in solution for the known benefit of binding capture-to-target molecules in large volumes for the obvious benefit of more rapid binding in solution as known in the art.

Regarding Claim 51, Hendrickson et al. teach the method of wherein the target molecule is a protein i.e. hTSH (page 523, left column, second full paragraph, lines 1-3).

Regarding Claim 52, Hendrickson et al. teach the method of wherein the target molecule is a protein i.e. hTSH (page 523, left column, second full paragraph, lines 1-3).

Regarding Claim 53, Hendrickson et al. do not teach the method wherein the sample is selected from the group consisting of blood, serum, sputum, urine, semen, cerebrospinal fluid, bronchial aspirate and organ tissue. However, Hendrickson et al. teach the method detects hTSH known to be present in blood (page 526, left column, last paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the method for detecting hTSH is a sample as taught by Hendrickson et al. to samples known to contain hTHS for the expected benefit of highly sensitive detection of hTSH (a clinically important target molecule) in blood as taught by Hendrickson et al. (page 528, last paragraph).

Regarding Claim 54, Hendrickson teach the method wherein the capture molecule is immobilized on a solid support (page 525, left column, second full paragraph, lines 1-6) but they do not teach the immobilization is via biotin labeled capture molecule bound to a streptavidin or avidin labeled support. However, biotin-labeled capture molecules immobilized via binding to a streptavidin or avidin labeled support were known and routinely practiced in the art at the time the claimed invention was made. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the immobilization of Hendrickson et al. with routinely practiced biotin-avidin immobilization for the known benefit of rapid and specific biotin-avidin immobilization.

Regarding Claims 55-56, Hendrickson et al. do not teach quantitation or detection using a non-primer probe having a fluorescent dye label (Claim 13) wherein the fluorescent dye label comprises two dyes (Claim 14). However, Gibson et al. teach quantitation of the amplified nucleic acid moiety using a detectable non-primer probe having a fluorescent dye label (page 996, right column lines 1-4) wherein the fluorescent dye label comprises two dyes, a reporter dye and a quencher dye which fluoresce at different wavelengths (page 996, right column lines 1-16). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the detection of Hendrickson et al. with the two-dye fluorescent detection of Gibson et al. wherein fluorescently labeled non-primer probes are detected to

quantitate PCR product by monitoring fluorescence emission and quenching (page 996, right column, lines 1-16) for the obvious benefit of detecting and quantitating amplified product over an extended period of time and for the expected benefit of accurate and time-saving detection as taught by Gibson et al. (page 995, right column, lines 1-5).

Regarding Claims 57-59, Hendrickson et al. do not teach the detector molecule is RNA and the RNA is reverse transcribed to form DNA before or during amplifying (Claim 17), at a temperature sufficient to dissociate the detector molecule (Claim 18) and at a temperature about 50 to about 70°C (Claim 19). However, Gold et al. teach aptamers are RNA (Column 14, lines 34-35) which are reverse transcribed before amplifying (Column 13, lines 39-51). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA of Hendrickson et al. with RNA as taught by Gold et al. based on target to be detected and desired results and to reverse transcribed the RNA to DNA before amplification as taught by Gold et al. and for the expected benefits of amplification using the polymerase chain reaction (Gold et al., Column 13, lines 40-42). Additionally, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to reverse transcribe the RNA detector molecule at a temperature sufficient to dissociate the detector molecule and specifically between 50 and 70°C for the obvious benefit of transcribing the RNA at temperature which prevents secondary structure of the RNA and for the expected benefit of partitioning the RNA detector molecule for identification as taught by Gold et al. (Column 1, lines 14-31).

Regarding Claim 60, Hendrickson et al. teach the method wherein the solid support is a 96-well thermowell microtitre plate which is placed into a thermal cycler for PCR amplification (page 525, left column, second full paragraph, lines 1-4 and fourth paragraph, lines 1-3) but they do not teach the solid support is a PCR tube. However, 96-well microtitre plates and PCR tubes were known and routinely practiced in the art for one-well/sample and one-tube/sample wherein reagent mixing and nucleic acid amplification for each sample is in isolation. It would

have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 96-wells PCR solid support of Hendrickson et al. with a single-well PCR solid support based the number of samples to be assayed, available equipment and experimental design for the obvious benefit of reducing the cost and labor involved with 96-format assays by performing single-format assays.

Regarding Claim 61-69, Hendrickson et al. teach the method wherein the target molecule is quantitated at a concentration equal to or less than 1000/mL (Claim 61) about 100 pg/ml (Claim 62); of about 1 pg/ml (Claim 63); of about 100 to about 5000pg/ml (Claim 64); of about 3 to about 5000 pg/ml (Claim 65); of about 0.04 of about 5000 pg/ml (Claim 66); of about 0.03 to about 5000 pg/ml (Claim 67); about 0.03 to about 1000 pg/ml (Claim 68) ; about 0.03 to about 100 pg/ml (Claim 69) (page 526, right column, first full paragraph and Fig. 4).

Response to Arguments

9. Applicant states that the instant invention is drawn to a method of quantitating or detecting the presence of a target molecule in a sample containing target and a nuclease wherein the method includes a step of washing to remove the nuclease. It is noted that the claim does not require the presence of nuclease. In contrast, the claim is drawn to "a sample which **may** contain the target molecule and a nuclease". Hence, the claims do not require the presence of nuclease.

Applicant argues that Hendrickson does not teach washing to remove nuclease, but instead suggests (at page 528, right column, second paragraph) that washing be eliminated to simplify the assay. The argument has been considered but is not found persuasive because the cited passage is merely a preferred embodiment of Hendrickson. Reading further on the page (right column, third paragraph), Hendrickson teaches an advantage of their capture method i.e. "analytes can be washed free of most potentially interfering substances". Hence, Hendrickson clearly teaches washing is important and a desired component of their method.

Applicant argues that Hendrickson et al, Gold et al nor Gibson et al teaches every element of the instant claims. Applicant's comments are noted, however, it is the combination, not the individual references that teach the instant invention. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant acknowledges the sensitivity of the Hendrickson method (i.e. 1 fg) but argues that Hendrickson does not teach the instantly claimed aptamer. Applicant further argues that Gibson does not teach the claimed sensitivity of aptamer detection using their real-time PCR and that Gold does not teach aptamer detection in a sample containing nuclease. Applicant's comment have been considered but are not found persuasive because the arguments attack the references individually, not their combination. Furthermore, it is noted that the claims do not require the presence of nuclease. Hence, arguments regarding the presence of nuclease are not commensurate in scope with the claims.

Applicant argues that the Office has not established a motive to combine the references. Applicant's arguments have been considered, but is not found persuasive because motivation has been clearly discussed above in the body of the rejection (reiterated from the previous office action). Applicant has not addressed the cited motivation, but instead argues that Hendrickson does not teach or suggest modification of their method and that Gold and Gibson do not expressly teach adding their method to that of Hendrickson.

Applicant cites Williams et al who teaches that the "utility of aptamer is often limited by their vulnerability to nucleases present in biological materials". The Williams reference has been reviewed. It is acknowledged that Williams et al teach aptamers are susceptible to nuclease. Williams et al have overcome this susceptibility by designing nuclease-resistant aptamers (Abstract). However, the fact that Williams et al have acknowledged and overcome the susceptibility problem of aptamers by designing nuclease-resistant aptamers does not negate the fact that Gold et al have also overcome the aptamer susceptibility (by washing) as evidenced by the fact that their method produces amplifiable aptamers (Gold et al, Column 25, lines 10-54). Furthermore, the nuclease-resistant aptamers of Williams require multiple synthesis steps (page 11285, right column) and utilize reagents that are not readily available (page 11290, left column, second full paragraph). As such, one of ordinary skill in the art would have been motivated to follow the aptamer method of Gold et al and to wash the aptamer complex thereby providing amplifiable nucleic acids for the obvious benefits of utilizing a simple method step (i.e. washing) to provide the desired results (i.e. amplifiable nucleic acids) as taught by Gold et al (Column 24, line 53-Column 25, line 9).

10. Claims 2, 4, 5, 8-14, 17-20 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cubicciotti (U.S. Patent No. 6,287,765, filed 20 May 1998) in view of Gibson et al. (Genome Methods 1996, 6: 995-1001).

Regarding Claim 46, Cubicciotti teaches a method for quantitating or detecting the presence of a target compound in a sample, the method comprising: exposing the sample to a capture molecule which binds to the target molecule to form a capture molecule-target molecule complex, adding to the complex a nucleic acid moiety containing a detector molecule wherein the detector molecule binds to the target molecule to form a capture molecule-target molecule-detector molecule complex, washing the complex, amplifying the nucleic acid moiety by PCR amplification, and quantitating or detecting the PCR amplified nucleic acid moiety (Column 229, lines 5-52). Cubicciotti teaches that the aptamers are amplified and detected using well known techniques (Column 155, lines 26-50) but they do not specifically teach the detection is via real time PCR. However, real-time PCR using detectable non-primer probes was well known and routinely practiced in the art at the time the claimed invention was made as taught by Gibson et al. Specifically, Gibson et al. teach a method for detecting a PCR amplified product with sequence-specific non-primer probes using real-time PCR (page 997, right column, page 1000, last paragraph and Table 1). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply real time PCR of Gibson et al to the detection of Cubicciotti and to detect and quantitate PCR products every 8.5 seconds (page 996, left column, lines 1-3) by detection of non-primer probe hybridization for the expected benefit of eliminating the agarose gel step and for the expected benefit of accurate and time-saving detection as taught by Gibson et al. (page 995, right column, lines 1-5).

Regarding Claim 2, Cubicciotti teaches the method further comprising washing the capture antibody: target molecule complex to remove unbound sample i.e. affinity chromatography (Column 229, lines 26-32)

Regarding Claim 4, Cubicciotti teaches the method wherein the capture antibody is bound to a solid support during step a or b (Column 221, lines 19-42).

Regarding Claim 5, Cubicciotti teaches the method wherein the capture antibody is in solution during step a or b (Column 229, lines 15-26).

Regarding Claim 8, Cubicciotti teaches the method wherein the target molecule is an organic compound having a molecular weight of about 100 to about 1000 grams/mole i.e. therapeutic peptide 7E3 (Column 228, lines 20-30).

Regarding Claim 9, Cubicciotti teaches the method of wherein the target molecule is a protein i.e. therapeutic peptide 7E3 (Column 228, lines 20-30).

Regarding Claim 10, Cubicciotti teaches the method of wherein the target molecule is a cytokine as claimed (Column 31, lines 1-17).

Regarding Claim 11, Cubicciotti teach the method wherein the sample is selected from the group consisting of blood, serum, sputum, urine, semen, cerebrospinal fluid, bronchial aspirate and organ tissue (Column 229, lines 5-15).

Regarding Claim 12, Cubicciotti teaches the method wherein the capture molecule is immobilized on a solid support via biotin (Column 163, lines 5-21).

Regarding Claims 13-14, Cubicciotti does not teach quantitation or detection using a non-primer probe having a fluorescent dye label (Claim 13) wherein the fluorescent dye label comprises two dyes (Claim 14). However, Gibson et al. teach quantitation of the amplified nucleic acid moiety using a detectable non-primer probe having a fluorescent dye label (page 996, right column lines 1-4) wherein the fluorescent dye label comprises two dyes, a reporter dye and a quencher dye which fluoresce at different wavelengths (page 996, right column lines 1-16). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the detection of Cubicciotti with the two-dye fluorescent detection of Gibson et al. wherein fluorescently labeled non-primer probes are detected to quantitate PCR product by monitoring fluorescence emission and quenching (page 996, right

column, lines 1-16) for the obvious benefit of detecting and quantitating amplified product over an extended period of time and for the expected benefit of accurate and time-saving detection as taught by Gibson et al. (page 995, right column, lines 1-5).

Regarding Claims 17-19, Cubicciotti teaches the method wherein the detector molecule is RNA and the RNA is reverse transcribed to form DNA before or during amplifying (Claim 17), at a temperatures well known in the art (Claims 18 & 19) (Column 153, line 33-Column 154, line 35). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply well known temperatures for reverse transcription and dissociation to the RNA detectors of Cubicciotti e.g. between 50 and 70°C for the obvious benefit of transcribing the RNA at temperature which prevents secondary structure of the RNA and for the expected benefit of partitioning the RNA detector molecule for identification.

Regarding Claim 20, Cubicciotti teaches the method wherein the solid support is a 96-well microtitre plate (Column 229, lines 15-26) but they do not specifically teach the 96-well plate is a PCR microtiter plate. However, 96-well microtitre plates and PCR tubes were known and routinely practiced in the art for one-well/sample and one-tube/sample wherein reagent mixing and nucleic acid amplification for each sample is in isolation. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 96-wells PCR solid support of Hendrickson et al. with a single-well PCR solid support based the number of samples to be assayed, available equipment and experimental design for the obvious benefit of reducing the cost and labor involved with 96-format assays by performing single-format assays.

11. Claims 24-45 and 47-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cubicciotti (U.S. Patent No. 6,287,765, filed 20 May 1998) in view of Gibson et al. (Genome Methods 1996, 6: 995-1001) as applied to Claim 46 above and further in view of Hendrickson et al. (Nucleic Acids Research, 1995, 23(3): 522-529).

Regarding Claims 24-45, Cubicciotti teaches the method of Claim 46 as detailed above but is silent regarding the concentration of the target molecule. However, detection of targets at a concentration of equal to or less than 5000 pg/ml was well known in the art at the time the claimed invention was made as taught by Hendrickson et al who teach a method similar to that of Cubicciotti wherein the target molecule is present at a concentration of equal to or less than 5000 pg/mL (page 526, right column, first full paragraph and Fig. 4). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the well known detection sensitivity of Hendrickson et al to detect target molecules at a concentration equal to or less than 1 pg/mL (Claims 14-16) about 100 to about 5000 pg/ml (Claims 27-29); of about 3 to 100 pg/ml (Claims 30-32); of about 0.4 to about 100pg/ml (Claims 33-35); of about 1 to about 100 pg/ml (Claims 36-38); of about 0.03 of about 100 pg/ml (Claims 39-41); of about 0.005 to about 1 pg/ml (Claims 42-44) as taught by Hendrickson et al (page 526, right column, first full paragraph and Fig. 4) of 5000 pg/ml or less for the obvious benefits of detecting clinically important low-copy number targets.

Response

12. Applicant argues that the cited passages of Cubicciotti do not teach the detection of a target molecule in a sample containing nuclease. The argument has been considered but is not found persuasive because, as stated above, the claims recite a sample which **may** contain a target and a nuclease. Hence the claims do not require nuclease and therefore, the argument is not commensurate in scope with the claims.

Applicant argues that Gibson and Hendrickson do not overcome the deficiencies of Cubicciotti. The argument has been considered but is not found persuasive for the reasons stated above regarding Cubicciotti.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (571) 272-0741. The examiner can normally be reached on 6:00 TO 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit: 1634
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